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To: **Examiner Rita Mitra Ph.D**
U.S. Patent and Trademark Office

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Serial No.: **09/549,463**

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Message/Comments: **Discussion items for interview on 8/6/03**

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Date: 8/4/2003

To: Rita Mitra Ph.D. (+1 (703) 746-5334)

From: Allen Turner (1(801)856-6011)

RE: US Patent Application 09/549,463; Attorney Docket No. 2578-4038.1

Purpose: FOR DISCUSSION PURPOSES ONLY - Items of discussion for interview of August 6, 2003 at 5:00 p.m.

Withdrawal of claims 103 and 104

The Office Action, at page 2, did not enter claims 103 and 104 because "the original elected claims encompass E1A protein only, and not E1B protein."

Independent claims 1 and 6 each included that the eukaryotic cell have a nucleic acid sequence "encoding at least one adenoviral E1 protein." These claims should thus include any and all E1 proteins including E1A and E1B. As such, the addition of claims 103 and 104 should not require further searches greater in scope than those required by the originally selected claims.

Summary of the Invention:

The present invention relates to the production of proteinaceous substances from eukaryotic cells in which at least one adenoviral E1 protein has been integrated into the genome. The integration of an E1 protein into the genome allows for the stable immortalization of these cells without any fear of losing the E1 protein during replication.

The Office Action, at lines 5-7 of page 5, remarks that:

> "Claims 1 and the dependent claims 77-86 thereto are directed to a process for the production of a proteinaceous substance in eukaryotic cell using a gene construct, having nucleic acid sequence that encodes an adenoviral E1 protein (claim 1) **or** a viral protein other than adenoviral protein (claims 77-86) **and** with a gene encoding a recombinant proteinaceous substance" (emphasis added).

Claim 1 recites, in part: "providing a eukaryotic cell having a nucleic acid sequence in the eukaryotic cell's genome, said nucleic acid sequence encoding at least

one adenoviral E1 protein." With the language of claim 1, the encoded adenoviral E1 gene is integrated into the genome of the cell.

In addition to the integrated E1 gene sequences, claim 1 further recites: "providing said eukaryotic cell with a gene encoding a recombinant proteinaceous substance." This gene may or may not be present on extra chromosomal nucleic acids such as plasmids, cosmids, infected viral DNA or other non-genomic sequences. The viral proteins other than adenoviral proteins of Claims 77-86 are meant to be specific embodiments of what a gene encoding a recombinant proteinaceous substance may include.

Rejections:

35 U.S.C. § 112 ¶ 1 Rejections

The Office Action, at page 3, rejects claims 77-86 under 35 USC 112 (enablement). The Applicants respectfully disagree and wish to raise the following items for discussion

1) In the description of the nature claim 1, the Office Action states that claim 1 is "directed to a process for the production of a proteinaceous substance in a eukaryotic cell using a gene construct, having nucleic acid sequence that encodes an adenoviral E1 protein." However, claim 1 has the nucleic acid sequence encoding an adenoviral E1 protein be present in the genome.

2) The Office Action, at page 6 states that the specification lacks "guidance as to the nature of functional derivatives that may be constructed." However, functional derivatives are not recited in the claim.

3) The Office Action, at page 6 lines 12-13, states that the claims are not enabled because "[n]o specific description is provided about the structure of influenza viral protein [or has] any activity of those proteins . . . been demonstrated." The structure and function of influenza proteins were well known in the art at the time of the invention (*see* attached PubMed printouts). Applicants need not provide what is well known in the art (*see* M.P.E.P. §§ 2164.01).

4) The Office Action states that the art is unpredictable. The specification provides 3 working examples. No inherent difference exists between the working examples (EPO, IgG heavy chain, and IgG light chain) and the viral proteins of claims 77-86. Furthermore, the example of IgG antibodies takes the form of a multimeric protein complex that is more complicated in post-translational assembly that the viral proteins thought to be unpredictable.

5) The Office Action states that there would be undue experimentation for influenza proteins. As the structure of the influenza proteins is known, all that should be required is for one skilled in the art to follow the protocol presented in Example 27. No experimentation should be required (*see* M.P.E.P. § 2164.06).

6) The Office Action presents a reference from 1994 as evidence of what is known by those skilled in the art. The present application is filed in 2000. In a fast moving field such as molecular biology, an art reference 6 years old is an inadequate demonstration of what would be known be one skilled in the art.

35 U.S.C. § 102(b) Rejection over Setoguchi et al.

The Setoguchi reference discloses the use of:

a) Hep3b cells to produce EPO from the DNA of a replication deficient adenovirus.
b) Cos-7 cells to produce EPO from the DNA of a replication deficient adenovirus.
c) 293 cells to produce replication deficient adenoviruses encoding EPO.

Claim 1 recites, in part, "providing a eukaryotic cell having a nucleic acid sequence in the eukaryotic cell's genome, said nucleic acid sequence encoding at least one adenoviral E1 protein."

Claim 6 recites, in part, "wherein said human cell has in its genome a sequence encoding at least one adenoviral E1 protein."

As Hep3b and COS-7 cells do not have a nucleic acid sequence encoding at least an E1 protein present in their genome, they cannot anticipate claims 1 and 6.

Regarding 293 cells, claim 1 recites in part "which eukaryotic cell further does not comprise a sequence encoding a structural adenoviral protein in its genome." However, 293 cells contain nucleotides 1 to 4344 of the adenovirus type 5 genome (Louis et al., *Cloning and sequencing of the cellular-viral junctions from the human adenovirus type 5 transformed 293 cell* line, 223 Virology 423 (1997)). Within this range of nucleotides, the gene for protein IX is encoded at nucleotides 3609 to 4031 (*Adenovirus type 5 left 32% of the genome (coordinates 0% to 32.39% as measured by <ad2>)*, NCBI Entrez Nucleotide accession number X02996 (deposited April 1999)). As such, the genome of 293 cells encodes protein IX. Furthermore, since protein IX is part of the adenovirus capsid important for thermostability, protein IX is a structural protein (Ghosh-Chudbury et al., *Protein IX, a minor component of the human adenovirus capsid is essential for the packaging of full length genomes*, 6(6) EMBO J. 1733 (1987)). Therefore, the 293 cells of Setoguchi do not anticipate the eukaryotic cell of claim 1 since the 293 cells encode an adenoviral structural protein in their genome.

With further regard to 293 cells, claim 6 recites in part: "where said human cell further does **not** produce structural adenoviral proteins" (emphasis added). As used in Setoguchi, the 293 cells do produce structural adenoviral proteins. Therefore, Setoguchi cannot anticipate claim 6.